REMARKS

Claims 76-86 are pending in this application.

The specification has been amended to properly identify trademarks by capitalizing each letter of the mark. In addition, the specification has been amended to correct certain editorial and typographical errors. No new matter has been added by the amendments.

I. THE OBJECTIONS TO THE SPECIFICATION SHOULD BE WITHDRAWN

The specification is objected to because the brief description of Figure 1 recites "A e B" instead of "A and B." In response, Applicant has amended the specification to correct this error.

The specification is also objected to because it uses trademarks without capitalizing the trademarks. In response, Applicant has amended the specification on page 7 to properly identify the trademarks.

For the foregoing reasons, Applicant submits that the objections to the specification are obviated and should be withdrawn.

II. THE CLAIM REJECTION UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 76-79 and 81-86 are rejected under 35 U.S.C. § 102(b) ("Section 102(b)") as allegedly being anticipated by Weichold *et al.* (WO 00/33654). Specifically, the Examiner alleges that Weichold *et al.* discloses using HIV protease inhibitors to treat diseases and conditions including cancer (see Office Action, page 3). The Examiner also alleges that Weichold *et al.* discloses that such HIV protease inhibitors include indinavir and can be used at the recited dosage (see Office Action, page 4). For the following reasons, Applicant disagrees.

1. The Legal Standard

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Further, the anticipating reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter. *PPG Indus.*,

Inc. v. Guardian Indus. Corp. 75 F. 3d 1558, 1564, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996).

In addition, a prior art reference that discloses a genus generally does not inherently disclose all species within that broad category. *Metabolite Laboratories, Inc. v. Laboratory Corp.*, 370 F.3d 1354, 1366 (Fed. Cir. 2004); *see also Eli Lilly v. Zenith Goldline*, 364 F.Supp.2d 820, 899 (S.D. Ind. 2005), *aff'd* 471 F.3d 1369 (Fed. Cir. 2006); *see also Atofina v. Great Lakes Chemical. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). Only where a prior art reference describes a limited class and where one skilled in the art "would, on reading [the prior art reference] at once envisage each member of this limited class" will the prior art reference describe each member of the limited class within the meaning of 35 U.S.C. 102. *In re Petering*, 301 F.2d 676, 681-682 (C.C.P.A. 1962). Indeed in *Atofina*, a temperature range of 200 degrees (150 ° to 350 °C) in the prior art disclosure was deemed to be too large a genus to disclose within the meaning of § 102 the individual temperature points within that range, and it was held that a disclosure in the prior art of a temperature range of 100 ° to 500 °C did not disclose within the meaning of § 102 a claimed range of 330 ° to 450 °C. 441 F.3d at 999-1000.

2. <u>The Claims Are Not Anticipated By Weichold *et al.*</u>

Weichold *et al.* discloses that HIV protease inhibitors (HIV-PIs) can be used to treat many disorders including cancer (see Abstract). Weichold *et al.* also discloses numerous classes encompassing vast numbers of HIV-PIs, as well as numerous examples of HIV-PIs, known in the art (see pages 25-26). Weichold *et al.* also discloses that HIV-PIs can be administered at a daily dose in a huge range of 0.05 to 100, and preferably about 0.5 to 20, milligrams per kilogram body weight (see page 29, lines 19-24). However, Weichold *et al.* does not disclose the use of indinavir at a daily dose of 1200 mg, as recited in claims 76 and 77.

The combination of using indinavir and administering indinavir at a daily dose of 1200 mg in the claimed methods is a distinct and novel species of the vast genera of HIV-PIs and daily dosages disclosed in Weichold *et al.* Applicant respectfully submits that this combination is not a species that would be "at once envisaged" from the disclosure of Weichold *et al.* by one of ordinary skill in the art. Instead, Weichold *et al.* discloses a vast number of HIV-PIs and classes thereof (more than three dozen) and a broad range of dosages

(assuming, as per the Examiner on page 4 of the Office Action, a human with a mass of 75 kg, the dosage ranges disclosed by Weichold *et al.* calculate to be 3.75 to 7500 or preferably 37.5 to 1500 mg per day). These genera of HIV-PIs (over 3 dozen) and dosages (over 1450 in the smaller preferred range) together constitute a huge number of combinations of particular HIV-PI and particular daily dosage. Out of the myriad possible combinations, there is nothing in Weichold *et al.* that teaches or guides one of ordinary skill in the art to particularly select indinavir as the HIV-PI and to particularly select 1200 mg as the daily dose. Both selections are necessary to arrive at the combination recited in claims 76 and 77 and both are missing from Weichold *et al.* Indeed, in *Atofina* even a temperature range of 200 degrees was deemed too large to be anticipatory of each degree within the range. *See* 441 F.3d at 999-1000. Therefore, as a matter of law, the genera disclosed in Weichold *et al.* do not anticipate the species recited in the pending claims. *See Atofina, Metabolite Laboratories, Eli Lilly, In re Petering.*

For the foregoing reasons, claims 76 and 77 and their dependent claims 78, 79 and 81-86 are not anticipated by Weichold *et al.* Withdrawal of the Section 102(b) rejection is respectfully requested.

III. THE CLAIM REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claim 80 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Weichold *et al.* as applied to claims 76-79 and 81-86. While the Examiner acknowledges that Weichold *et al.* does not specifically teach administering a composition comprising both indinavir and nelfinavir (see Office Action, page 5, fourth paragraph), the Examiner alleges that one of ordinary skill in the art would have been motivated to administer a combination of agents, such as indinavir and nelfinavir, because both are useful for treating cancer or tumors as taught by Weichold *et al.*, and that one of ordinary skill in the art would have had a reasonable expectation of success that the combination treatment would result in the intended use of treating cancer or tumors (see Office Action, paragraph bridging pages 5 and 6). For the following reasons, Applicant disagrees.

1. The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have

been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *See* 35 U.S.C. § 103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *See KSR International Co.*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467; *see also* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* ("Examination Guidelines"), Federal Register, Vol. 72, No. 195, October 10, 2007, pages 57527-57528. The Supreme Court also stated that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...." *KSR International Co.*, 127 S.Ct. at 1741, 82 U.S.P.Q.2d at 1396. The Supreme Court went further to clarify that "this is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* Furthermore, the relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350, 21 U.S.P.Q.2d 141, 1943 (Fed. Cir. 1992). *In re Jones* involved an obviousness rejection of a claim to a specific compound, the 2-(2'-aminoethoxy)ethanol salt of 2-methoxy-3,6-dichlorobenzoic acid (dicamba), as obvious in view of, *inter alia*, a prior art reference disclosing a genus which encompassed the claimed salt. *Id.* The court reversed the Board's rejection, reasoning that the prior art reference encompassed a "potentially infinite genus" of salts of dicamba and listed several such salts, but that it did not disclose or suggest the claimed salt. *Id.* The court reached a similar conclusion in *In re Baird* when considering the patentability of bisphenol A in view of a prior art reference that disclosed a generic diphenol formula which contains a large number of variables and which encompasses bisphenol A. 16

F.3d 380, 382, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994). The court in *In re Baird* noted that there was nothing in the disclosure of the prior art reference to suggest the selection of specific variables to arrive at bisphenol A, particularly when there is a teaching away of the selection of bisphenol A. *Id.*

2. Claim 80 is Patentable Over Weichold *et al.*

Claim 80 is nonobvious over Weichold *et al.*, by virtue of its dependency upon claims 76 and 77, which in turn are nonobvious over Weichold *et al.* for the following reasons.

As discussed above, Weichold *et al.* does not teach or suggest selecting indinavir as the particular HIV-PI, to be administered at a daily dose of 1200 mg to a human to treat cancer, out of the genus of myriad possibilities of HIV-PI and dosage disclosed in Weichold *et al.* Moreover, Weichold *et al.* teaches away from administering indinavir at a daily dose of 1200 mg. While Weichold *et al.* discloses that the HIV-PIs can be administered at the broad dosage range of 0.05 to 100, and preferably 0.5 to 20, mg per kg body weight per day (see Weichold *et al.*, page 29, lines 22-24), which calculates to be 3.75 to 7500, and 37.5 to 1500, mg per day (assuming, per the Examiner on page 4 of the Office Action, a 75 kg human), the guidance given by Weichold *et al.* for selecting within these dosage ranges is to use the dosage at the same concentrations that are achieved in humans under HIV therapy (see Weichold *et al.*, page 26, line 27 to page 27, line 2; and page 29, lines 19-21). As shown by the "British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy," HIV Med., 2000, 1(2):76-101 (made of record as reference C06 in the Supplemental Information Disclosure Statement filed September 29, 2006), one of ordinary skill in the art would have understood at the time the invention was made that the commonly used daily dose of indinavir in HIV therapy is 2400 mg (800 mg, three times a day) (see page 86, Table 5), which is much greater than the 1200 mg recited in claims 76 and 77. Weichold *et al.* does not teach or suggest administering to a human subject a particular HIV-PI at daily dosages that are lower than those commonly used in HIV therapy with that HIV-PI. Therefore, one of ordinary skill in the art would have no reason to use indinavir at a daily dose such as 1200 mg, which is much lower than that commonly used in HIV therapy, to treat cancer, nor would such a person have a reasonable expectation of efficacy in the use of such dosage.

Moreover, Weichold *et al.* also fails to provide a reasonable expectation of success in the use of indinavir to treat a tumor or block cell migration in a human subject for the additional reason that Weichold *et al.* does not disclose any data convincing of efficacy in such use. In particular, although *in vitro* data regarding indinavir's effects on PMBCs (peripheral blood mononuclear cells) can be found in Figures 2 and 3 of Weichold *et al.*, Weichold *et al.* does not disclose any *in vivo* data for indinavir, unlike for ritonavir. The only data in Weichold *et al.* relating to indinavir concerns *in vitro* studies of indinavir's pro-survival effects on PMBCs exposed to "stress factors" such as IFN-alpha, IFN-gamma and TNF-alpha, which are known to be involved in HIV pathogenesis (see Example XIII at pages 49-51). Thus, the skilled artisan would not view the disclosure of Weichold *et al.* as giving rise to any reasonable expectation of success in using indinavir to treat cancer. This is particularly true in view of the fact that, although both ritonavir and indinavir are HIV-PIs, it was known in the art that their mechanisms of action and effects appeared to be different from each other. For example, U.S. Patent No. 6,506,555 ("the '555 patent") (made of record as reference A01 in the Information Disclosure Statement filed September 15, 2005) discloses that ritonavir inhibited footpad swelling in mice injected with LCMV (lymphocytic choriomeningitis virus) and the direct lysis *ex vivo* after systemic infection, both of which measure the intensity of CTL (cytotoxic T lymphocyte) response (see col. 8, lines 36-47). In contrast, indinavir did not reduce swelling of the footpad nor did it reduce the direct lysis *ex vivo* (see the '555 patent, col. 8, lines 22-27). Thus, indinavir does not act like ritonavir in this animal model and was found ineffective at doses comparable to those doses of ritonavir effective in this model. Because this difference in actions between ritonavir and indinavir was already known in the art, one of ordinary skill would not predict indinavir to act like ritonavir. Thus, the teachings relating to ritonavir in Weichold *et al.* do not give reason to expect that one could successfully use indinavir to treat cancer, or that such will be a predictable solution to the problem of treating cancer. Therefore, one of ordinary skill in the art at the time the invention was made would have no reason to expect that indinavir would be useful to treat cancer, since the mechanism of action and effects of indinavir are different from those of ritonavir such that the substitution of ritonavir with indinavir would not be expected to yield any predictable results.

In addition, Applicant submits that the Examiner has not established a *prima facie* case of obviousness. Rejections based on obviousness cannot be sustained by mere

conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *See KSR*; Examination Guidelines, paragraph bridging pages 57528-57529. Specifically, the Examination Guidelines set forth seven rationales that an Examiner can use to support rejections under 35 U.S.C. § 103. However, Applicant submits that none of these rationales can support a conclusion of obviousness of the claimed invention.

First, Applicant submits that the claimed invention is not the result of combining prior art elements according to known methods to yield a predictable result (see Examination Guidelines, rationale (A)). As discussed above, there is nothing in Weichold *et al.* to give reason to use the particular HIV-PI indinavir at the particular dosage of 1200 mg, much less with predictable results. In fact, one of ordinary skill at the time the invention was made would understand that indinavir has different actions than ritonavir, and that Weichold *et al.* taught away from using indinavir at the daily dosage of 1200 mg, since it is much less than the dosage used in humans for HIV therapy.

Second, Applicant submits that the claimed invention is not the result of a simple substitution of one known element for another to obtain a predictable result (see Examination Guidelines, rationale (B)). While indinavir and ritonavir are both HIV-PIs, they have different actions and thus, would not yield predictable results, much less at a dosage counter-indicated by Weichold *et al.*

The third rationale set forth in the Examination Guidelines concerns the use of known technique to improve similar devices (methods, or products) in the same way (see Examination Guidelines, rationale (C)). Applicant submits that this rational is not applicable to the claimed invention.

Fourth, Applicant submits that the claimed invention is not the result of applying a known technique to a known device (method, or product) ready for improvement to yield predictable results (see Examination Guidelines, rationale (D)).

Fifth, Applicant submits that the claimed invention is not "obvious to try" where the invention is chosen from a finite number of identified, predictable solutions with a reasonable expectation of success (see Examination Guidelines, rationale (E)). The selection of indinavir as the particular HIV-PI and the selection of 1200 mg as the particular dosage for cancer treatment are not the result of choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. As discussed above, Weichold *et al.*

discloses a large number of HIV-PIs and a broad range of dosages, which together constitute a huge number of combinations of particular HIV-PI and particular daily dosage. One of ordinary skill would not know which HIV-PI and what dosage to select out of the myriad possible combinations and have a reasonable expectation of success for cancer treatment. Moreover, one would not have had a reasonable expectation of success for the additional reason that Weichold *et al.* taught away from using a 1200 mg daily dosage for indinavir, and presents no data convincing of cancer therapeutic efficacy for indinavir, as discussed above.

Sixth, Applicant submits that the claimed invention is not a variation prompted by known work in another field of endeavor based on design incentives or other market forces, much less such a variation that is predictable to one of ordinary skill in the art (see Examination Guidelines, rationale (F)). The Examiner has not come forth with any evidence to this effect.

Finally, Applicant submits that the claimed invention is not the result of some teaching, suggestion or motivation in the prior art that would have led one of ordinary skill in to modify the prior art reference or to combine prior art reference teachings (see Examination Guidelines, rationale (G)). To the contrary, as discussed above, Weichold *et al.* gives no guidance to select such a dosage, and in fact, teaches away from using such a low dose of indinavir.

For the foregoing reasons, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness with respect to claims 76 and 77, on which claim 80 depends. Moreover, there are additional reasons why dependent claim 80 is patentable over Weichold *et al.*, discussed below.

Contrary to the Examiner's allegation, one of ordinary skill in the art at the time the invention was made would have no reason to expect that nelfinavir would be useful to treat cancer, since the '555 patent also teaches that the mechanism of action and effects of nelfinavir are different from that of ritonavir. The '555 patent discloses that nelfinavir, like indinavir and unlike ritonavir, did not inhibit footpad swelling in mice injected with LCMV nor did it reduce the direct lysis *ex vivo* (see col. 8, lines 22-27). Like indinavir, nelfinavir also does not act like ritonavir in this animal model. Because this difference between ritonavir and nelfinavir was already known in the art, the teachings relating to ritonavir in Weichold *et al.* do not teach or suggest to one of ordinary skill that one could successfully use nelfinavir to treat cancer. Contrary to the Examiner's allegation, and in view of the

discussion above regarding indinavir, one of ordinary skill in the art at the time of the invention would have no reason to combine indinavir and nelfinavir to treat cancer or tumors, much less with a reasonable expectation of success. Thus, claim 80 is patentable over Weichold *et al.* Withdrawal of the Section 103(a) rejection is respectfully requested.

CONCLUSION

Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same. If any additional fee is required for the submission of this response, please charge any such fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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32,605
Adriane M. Antler (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939

Enclosure